Remarks

Currently Claims 1-23, 25, 27-28 and 30-34 are pending. Claims 24, 26, 29 and 35-36 are cancelled herein. Claims 1, 22 and 23 are amended herein. Entry of the foregoing amendments is respectfully requested. Applicants expressly reserve the right to file one or more continuation applications directed toward the subject matter cancelled by this amendment.

Applicants acknowledge with appreciation the Examiner's indication that the claimed invention is free of the prior art.

Section 112, Second Paragraph Rejections Overcome

Claims 1-36 currently stand rejected under 35 U.S.C. §112, second paragraph, the Office Action stating that the claims are indefinite. Specifically, the Examiner has objected to the terms "physiologically functional derivative." While Applicants do not agree with the Examiner's rejection, claims 1 and 22 have been amended to remove the objected term for the purpose of expediting allowance of the claimed subject matter. Withdrawal of this rejection is respectfully requested.

Claim 22 further stands rejected under §112, second paragraph, the Office Action stating that the claim is indefinite for reciting "and pharmaceutically acceptable salts...". Applicants respectfully submit the claim 22 as amended utilizes proper Markush form beginning with "selected from the group consisting of" and use of the conjunction "and" before the final member. This language is clearly recognized as alternative format. MPEP2173.05(h) ("One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being 'selected from the group consisting of A, B and C'.") (emphasis added). Withdrawal of the rejection is therefore respectfully requested.

Claim 23 further stands rejected under 112, second paragraph, the Office Action stating that the claim is indefinite for reciting a composition containing a compound of formula (I) without a further ingredient. Applicants expressly disagree that the claim in its original form is indefinite. However, for the purpose of expediting allowance of the claimed subject matter, Applicants have incorporated the limitations of claim 24 into claim 23, thereby obviating the Examiner's rejection. Withdrawal of the rejection is respectfully requested.

Section 112, First Paragraph Rejections Overcome

Claims 1-36 currently stand rejected under 35 U.S.C. §112, first paragraph, the Office Action stating that the specification is not enabling for "physiologically functional derivatives." While Applicants do not agree with the Examiner's rejection, the previously discussed amendment of claims 1 and 22 obviates the rejection. Withdrawal of this rejection is respectfully requested.

Claims 1-36 further stand rejected under §112, first paragraph, the Office Action stating that the specification is not enabling for "solvates." While Applicants do not agree with the Examiner's rejection, the amendment of claims 1 and 22 obviates the rejection. Withdrawal of this rejection is respectfully requested.

Claims 26-31 further stand rejected under §112, first paragraph, the Office Action stating that the specification is not enabling for a method of treating a condition mediated by Plk or for the various cancers recited. While Applicants do not agree with the Examiner's rejection of claims 26 and 29, those claims are cancelled and thus the rejection is moot. The rejection of claims 27-28 and 30-31 is respectfully traversed.

The Examiner has requested that Applicants' review the PTO website at address: <<http://www.uspto.gov/web/offices/pac/dapp/1 pecba.htm#7>>. Applicants are unable to access this webpage and accordingly are unable to respond to this point.

Preliminarily, it is noted that the rejection does not state that the specification fails to teach how to make the claimed compounds and the rationale for the rejection is limited to failure to teach how to use the claimed compounds. Accordingly, the Examiner has implicitly acknowledged that the application enables one skilled in the art how to make the claimed compounds. The following remarks address only the "how to use" aspect of the enablement test. If the Examiner intended to reject the claims for failure to teach how to make the claimed compounds, the rejection is unclear and precludes response.

"The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.... It is incumbent on the PTO to explain why it doubts the truth or accuracy of any statement in a supporting

disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." MPEP 2164.04.

It is respectfully submitted that the rejection of claims 30-31 fails to meet this burden of providing evidence to establish why one skilled in the art would be unable to use the claimed methods. Claims 30 and 31 are drawn to methods for inhibiting proliferation of a cell and methods for inhibiting mitosis in a cell, respectively. The reasons for rejection are all directed toward utility in the treatment of conditions mediated by Plk and cancers. The rejection contains no reasoning why one skilled in the art would question the asserted utility with respect to claims 30-31. The rejection of claims 30-31 is therefore improper and withdrawal is respectfully requested.

Similarly, there appears to be no separate analysis of the enablement of claims 27 and 28. Broad generalizations that "it is beyond the skill of oncologists today to get an agent to be effective against cancers generally" (Office Action page 14) is inapplicable to claims directed toward specific types of neoplasms, i.e., those that are susceptible to Plk. In particular, there is no rationale provided for the Examiner's assertion that one skilled in the art would doubt the asserted utility in the neoplasms recited in claim 28. No evidence is provided that the compounds which are shown to inhibit Plk (see the enzyme data provided in the specification) and which are shown to inhibit cellular proliferation in several relevant cancer cell lines would be useful for treating neoplasms susceptible to Plk or the specifically enumerated neoplasms of claim 28. Accordingly the Examiner has failed to meet his burden in rejecting these claims.

Applicants respectfully submit that consideration of all relevant evidence regarding enablement establishes that one skilled in the art would be able to use the claimed invention without undue experimentation. The Examiner has recited the relevant factors from *In re Wands* for evaluating undue experimentation, but the rejection does not properly apply those factors to the instant specification or provide the necessary objective evidence to establish a reasonable basis why one skilled in the art would doubt the asserted utility of the claimed compounds.

In the present case, the claims are directed to methods of treating neoplasms that are susceptible to Plk. The claims do not recite "any and all cancers, infections,

inflammatory and autoimmune diseases" as suggested by the Examiner (pg 16). The Examiner is referred to the language of claim 27 which specifically states "neoplasm susceptible to Plk". The background of Plk and its involvement in the cell cycle (mitosis) is provided in the specification. The specification also includes a description at page 34, of specific neoplasms which were known as if the filing date to be susceptible to Plk. The claim scope sought finds full support in the written description of the specification, which includes the description of the neoplasms which are susceptible to Plk as well as both enzyme and cellular proliferation data demonstrating inhibition of Plk and cell proliferation in several cell lines, for the majority of exemplified compounds. Accordingly, the scope of the claims is commensurate with the scope of the description.

The relevant art for claims 27-28 is oncology and Applicants submit that the level of ordinary skill in the art is high. The rejection does not indicate the level of skill under which enablement was analyzed. The level of one of ordinary skill in the art is highly pertinent to the question of whether undue experimentation is required to practice the claimed invention. *In re Wands* and MPEP 2164.01(a). Failure to analyze enablement in light of the level of skill in the art is improper.

It also appears that the rejection does not consider the scope and content of the knowledge in the art regarding the role of Plk in cancer. The Examiner has pointed to Ahmad, *FASEB J.* **18**:5-7, which is only one of many articles that demonstrate the state of knowledge in the art with respect to the correlation between Plk inhibition and various cancers. Submitted herewith is a review of Plk and Oncogenesis, (F. Eckerdt, et al., *Oncogene* (2005) **24**:267-276) which demonstrates the state of the knowledge in the art at the time of filing. At page 269, Eckerdt et al., list numerous human tumor types in which Plk has been suggested to be a marker for proliferation. Among those tumor types listed are:

non-small cell lung cancer (citing Wolf et al., (1997) *Oncogene* **14**:543-549),

head and neck squamous cell carcinomas (citing Knecht et al., (1999) *Cancer Res.* **59**:2794-2797),

esophageal carcinoma (Tokumitsu et al., (1999) *Int. J. Oncol.* **15(4)**:687-692),

oropharyngeal carcinomas (citing Knecht et al., (2000) *Int. J. Cancer* **89**:535-536),

melanomas (Strebhardt et al., 2000) *JAMA* **283**:479-480),

breast cancer (Wolf et al., (2000) *Pathl. Res. Pract.* **196**:753-759),
endometrial carcinomas (Takai et al., (2001) *Cancer Lett.* **169(1)**:41-49),
colorectal cancer (Macmillan et al., (2001) *Ann. Surg. Oncol.* **8**:729-740) and Takahashi et al., (2003) *Cancer Sci.* **94**:148-152),
ovarian cancer (Takai et al., (2001) *Cancer Lett.* **169(1)**:41-49 and Weichert et al., (2004) *Br. J. Cancer* **90**:815-821),
pancreatic cancer (Gray et al., (2004) Mol. Cancer Ther. **3**:641-646),
prostate carcinomas (Weichert et al. (2004) *Prostate* **60**:240-245 and the Ahmed article pointed out by the Examiner), and
papillary carcinomas (Ito et al., (2004) *Br. J. Cancer* **90**:414-418).

In addition, Eckerdt states that Plk1 expression correlates to the metastatic potential of tumors (*citing* Kneisel et al., (2002) *J. Cutan. Pathol.* **29**:354-358).

Applicants acknowledge that the Eckerdt, article was published after the priority filing date. However, the numerous articles cited therein for support of the correlation between Plk and various tumors were published earlier –most before Applicants' priority filing date.

The Ahmad article cited by the Examiner provides further support of the knowledge in the art, stating:

> "Plk1 expression has prognostic value for predicting outcomes in patients with several cancers, including non-small cell lung cancer, squamous cell carcinomas of the head and neck, melanomas, oropharyngeal carcinomas and ovarian and endometrial carcinomas." Ahmad, (2004) pg 5 (see references cited therein).

The Examiner is also referred to the following articles which further establish that one of ordinary skill in the art would have no reason to doubt the asserted utility of the claimed invention.

Yuan, J., et al., (1997) *Am. J. Pathology* **150(4)**:1165-1172 ("Plk protein was found expressed in the nuclei of tumor cells from lung and breast cancers as well as in several tumor cell lines." Abstract) (abstract provided)

Holtrich, U, et al,. (1994) *Proc. Nat. Ac. Sci. USA* **91(5)**:1736-1740 ("Tumors of various origin (lung, colon, stomach, smooth muscle, and esophagus as well as non-Hodgkin lymphomas) expressed high levels of Plk transcripts in about

80% of the samples studied, whereas Plk mRNA was absent in surrounding tissue, except for colon." Abstract) (copy provided)

The Examiner is compelled to consider all of the evidence provided by Applicants' in support of the claimed invention. MPEP 2164.01 (any part of the application can support an enabling disclosure). It appears from the rejection that the Examiner did not consider all of the teaching provided by Applicants' disclosure. In particular, it appears that the Examiner did not consider the cellular proliferation data provided. Applicants have provided cellular proliferation data in cell lines corresponding to breast cancer (MCF7 and MDA435), colon cancer (HCT116, RKO and Colo205), prostate (PC3), osteosarcoma (SAOS2), and non-small cell lung cancer (H460). Inhibition of cellular proliferation is an art recognized model for assessing activity in various cancers.

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." MPEP 2163.04 *citing In re Fisher.* In view of the substantial guidance and direction in Applicants' specification, the working examples providing enzyme and inhibition of cellular proliferation, the advanced state of the knowledge in the art correlating Plk inhibition and treatment of human tumor types and the high level of skill in the art, it is respectfully submitted that there is a high degree of predictability in the art that Plk inhibitors may be used to treat a variety of neoplasms.

Lastly, the level of experimentation necessary to determine the effects on cellular proliferation for a given compound in a given cell line is routine in the art. Even complex experimentation is not undue if the art typically engages in such experimentation. MPEP 2164.01 and *In re Wands. In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), is on point with the facts of the instant case. In *Wands*, the claims were to immunoassay methods using a generic class of antibodies. A single hybridoma secreting a single antibody was deposited. The court reversed the examiner's enablement rejection because the application included considerable guidance and direction, the level of skill in the art was high, and all of the methods needed to practice the invention were known in the art, such that those skilled in the art could produce and screen hybridomas secreting other monoclonal antibodies without undue experimentation. Even though not all hybridoma fusions

would be successful, the specification was nevertheless enabling. The court determined that "enablement is not precluded by the necessity for some experimentation such as routine screening.... The key word is 'undue,' not 'experimentation'." *Wands* at 736-737.

The art at the time of filing, included the knowledge that enzyme and cellular proliferation assays could be used to evaluate the activity of a given compound for particular kinases, including Plk and that those assays are recognized models for assessing activity in human tumor types. There were, at the time of filing, known methods for conducting such screening using automated high-throughput screening capable of quickly evaluating activity of thousands of compounds against a plethora of different targets. Methods for conducting such screens are also provided in the Applicants' specification at pages 182-184. Inasmuch as this experimentation is routine in the art and described in the specification, it does not constitute undue experimentation pursuant to *In re Wands*.

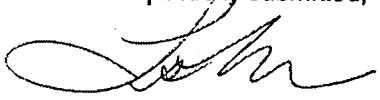
It is therefore respectfully submitted that all of the Wand's factors support Applicants position that undue experimentation would not be required in the instant case. The pending claims are fully enabled by the specification and withdrawal of this rejection is therefore respectfully requested.

Supplemental IDS and PTO-1449

Filed concurrently herewith is a supplemental IDS and PTO-1449. The Examiner's consideration of the references cited and return of an initialed PTO-1449 with the next communication from the Office is respectfully requested. Applicants are submitting an english language translation of the claim of DE10011530A1, already of record. US Patent Nos. 6362178, 6566360, 6890922, 7122540, and US Pubilcation No. 2006/0189615, are indicated as corresponding to EP 1 174 431 A2, already of record. Copies of journal articles cited above, that were obtainable by the response due date, are also included in the PTO-1449.

Applicants respectfully submit that the instant application is in condition for allowance, which action is respectfully requested. The Examiner is invited to contact the undersigned at (919) 483-8222, to discuss this case, if desired.

Respectfully submitted,



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Date: 6 December, 2007

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